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EDITORIAL

Albumin administration for complicated spontaneous bacterial peritonitis — Truth be (re)told!

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Albumin administration in patients with decompensated cirrhosis has been studied both in the context of prophylaxis and management. Albumin is synthesized exclusively by the liver, at a rate that matches its daily degradation (13.0 g/day). It is the most abundant plasma protein (concentration 3.5–5.0 gm/dL, approximately 50% of all plasma proteins). More importantly, it accounts for 75% of plasma oncotic pressure; hence, it has a vital role in plasma volume expansion. It has several homeostatic functions, too, such as it acts as a scavenger (bile salts, bilirubin, heavy metals etc.), antioxidant (circulates in reduced state with a free thiol group at Cys 34 residue, scavenges reactive oxygen and nitrogen species) and immune modulator (modulates innate immune response to sepsis through prostaglandin E2 [PGE2], pathway).

The indication for the use of albumin in decompensated cirrhosis is highlighted in Table 1. In spite of recommendations being endorsed by major guidelines (European Association for the Study of the Liver [EASL]/American Association for the Study of Liver Diseases [AASLD]), the evidence for albumin use (dose, timing and duration) has been masked by the lack of robust evidence through well-conducted clinical trials.

This brings us to the observational study regarding the use of albumin in patients with complicated spontaneous bacterial peritonitis (SBP) (all patients had acute kidney injury [AKI] at baseline) published in this issue of *Indian Journal of Gastroenterology* [1]. This study was conducted at a tertiary care center in northern India and suggests "relook" at current guidelines on the use of albumin for patients with SBP. The authors performed multiple interventions (some rather superfluous like the assessment of renal resistive index) in a cohort of patients with SBP, all of whom had AKI at baseline (grade of injury not specified). The authors divided the cohort into two: those who received albumin as per guideline recommendations (1.5 g/kg on D1 and 1 g/kg on D3) and those who received the albumin at a reduced dosage (0.75 g/kg on D1 and 0.5 g/kg on D3). The authors found the guideline recommended the dose to produce functional circulatory overload in every single patient they treated ($n = 31$). This mandated the cessation of infusion, need for diuretic therapy and effectively reduced the dose of albumin for this group of patients both D1 and D3. The comparative cohort had a much lower incidence of this complication (two out of 32 patients). The authors found no difference in hard outcome measures (resolution of SBP, resolution of AKI progression of AKI, and mortality during hospitalization and day 28). The important message from this observational study is that possibly a lower dose of albumin administered at slower infusion rate may mitigate respiratory distress due to circulatory overload in this set of patients (Table 2). The practice in Western hemisphere is of course to administer albumin for this indication in the dose mentioned earlier. The authors explain the difference to lower body mass index (BMI), cardiac chamber size and different body fluid compartment sizes in Asians (especially Indians) vis-à-vis Caucasians. However, this is representative.

Even though this study gives an important message, some drawbacks in the observation must be emphasized:

- Small size cohort, underpowered to draw firm conclusion.
- Difficult to have the investigators blinded with respect to amount/volume of albumin infused.
- Patients do not just have a diagnosed complicated SBP; they have AKI, too, which is a completely different scenario with respect to volume status and response to fluid therapy.

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Table 1 Indication of albumin infusion in patients with decompensated cirrhosis

Established	Potential
Large-volume paracentensis[x] (8 g/L of ascitic fluid removed)	Moderate-volume paracentensis
HRS-AKI[x] (1 g/kg/day × 2 days followed by 20–40 g/day)	Non-SBP infections
SBP[x] (1.5 g/kg on D1 and 1 g/kg on D3)	Hepatic encephalopathy
	Hyponatremia
	Fluid resuscitation in cirrhotics[+]
	HRS-NAKI[+]

[x]The suggested dose and timing by most guidelines is at best empiric

[+]Contentious indications, may be potentially hazardous

HRS hepatorenal syndrome, *AKI* acute kidney injury, *SBP* spontaneous bacterial peritonitis, *NAKI* non-acute kidney injury

- About 80% of the patients in the cohort had cirrhotic cardiomyopathy at baseline with systolic dysfunction being dominant component (45% of those who had cirrhotic cardiomyopathy).
- Every single patient who developed circulatory overload responded to intravenous diuretics and was ready for D3 infusion.
- Use of pressors/splanchnic vasoconstrictors (especially Terlipressin), which could make the interpretations of findings difficult.
- An earlier study from the same center using a higher dose of albumin, administered at high flow rate, failed to produce circulatory overload, even though the patients with SBP were very few in that study.

This leads us to the broader question of when and how much of albumin should be administered to patients with decompensated cirrhosis. We feel that this approach of albumin administration should be nuanced**.** The administration of large amounts (40–60 g/day) over a relatively short period of time (1–2 h) (as exemplified in the long-term albumin administration in decompensated cirrhosis [ANSWER] trial) might not produce untoward effect of circulatory overload/respiratory distress in a stable patient [2].

The same or much lower amount (by weight or volume) may produce new respiratory adverse events (albumin to prevent infection in chronic liver failure [ATTIRE] trial) if patient has an "inflamed milieu" or "endothelial dysfunction" [3]. The problem may or may not be compounded by the use of vasoconstrictors, e.g. Midodrine (midodrine-albumin in cirrhotic patients awaiting liver transplantation [MACHT trial]), which did not report an increased risk of volume overload or respiratory adverse events [4] or Terlipressin (CONFIRM trial), in which 15% of the albumin terlipressin arm developed respiratory failure [5]. From pathophysiologic and mechanistic standpoint, this is not difficult to explain — the timing of albumin administration in relation to the onset of actual event (in this case sepsis or circulatory dysfunction) could be critically important. One must also realize that in diseased states, native albumin as well as exogenously administered albumin, can get modified (ischemia-modified albumin) or oxidized (human non-mercaptalbumin HNA1 and HNA2). These forms of albumin cannot perform the pleiotropic functions mentioned earlier.

Therefore, it is best to concede that, even though albumin is one of the most commonly used "drug" in contemporary Hepatology practice, our understanding of its myriad forms and properties is far from complete.

Declarations

Conflict of interest DK and KB declare that they have no conflict of interest.

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Table 2 Amount, rate and duration of infusion in the two cohort of current study

	Amount of albumin		Rate of infusion		Duration of infusion	
Standard dose	Day 1	0.77 g/kg	Day 1	1.4 mL/min	Day 1	185 min
	Day 3	0.65 g/kg	Day 3	1.0 mL/min	Day 3	235 min
Reduced dose	Day 1	0.75 g/kg	Day 1	0.7 mL/min	Day 1	360 min
	Day 3	0.5 g/kg	Day 3	0.5 mL/min	Day 3	360 min

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